REMARKS

Reconsideration and withdrawal of the rejections of this application and consideration and entry of this paper are respectfully requested in view of the herein remarks and accompanying information, which place the application in condition for allowance.

1. Status of Claims and Formal Matters

Claims 1-15, 17, 22-29 and 44-47 were under consideration in this application. Claims 1-15, 17, 22-29 and 44-47 have been cancelled. Claims 48-71have been added. Support for the claim amendments is found throughout the specification as originally filed. No new matter has been added by this amendment.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims were in full compliance with the requirements of 35 U.S.C. § 112. The amendments of the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

2 The Rejections Under 35 U.S.C. § 112 Are Overcome

Claims 10 and 26 are rejected to under 37 CFR 1.75(c) as being in improper form. Claims 10 and 26 have been cancelled, thereby obviating the rejection.

3 The Rejections Under 35 U.S.C. § 103 Are Overcome

Claims 1-15, 17, 22-25, 28, 29 and 44-47 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,061,639 to Lung *et al.* (hereinafter "Lung") in view of U.S. Patent No. 5,320,969 to Bauer *et al.* (hereinafter "Bauer"). These rejections are respectfully traversed. The cited references do not make the instant invention obvious.

In responding to the arguments submitted in the 37 CFR 1.132 by Dr Hälg ("the Hälg Declaration"), the Office Action asserted that it would have been obvious to apply the indicators in Bauer to the volumetric determination system disclosed in Lung. However, the Office Action did not address the essential arguments in the Hälg Declaration which asserted that the methods claimed in the present application are inherently different than the methods disclosed in Lung.

As it appears that that there may have been some confusion over the nature and scope of the claims, the claims have been amended to address the essential embodiments of the present invention. In the subsequent discussion, the amended claims will be compared with the references cited in the Office Action.

Independent claims 48 and 49 were addressed in detail in the Hälg Declaration. It was pointed out that there were various problems associated with making accurate volumetric determinations, particularly for very small volumes. A particular problem was that the dyes had to be present in high concentrations when measuring small volumes (e.g., the nanoliter range). In such instances, the dyes may stick to the walls of the pipette. Moreover, the concentrated dyes would potentially alter the properties of the aqueous diluent, thus making it impossible to apply Beer's Law. To overcome these problems, Applicants developed a method of generating the dyes *in situ* by adding a solution of metal ions to a diluent containing a particular, polydentate chromogenic ligand. Rapid and irreversible complexation between the metal ions and the polydentate chromogenic ligand results in the generation of highly colored complexes. As stated in the Hälg Declaration:

> A goal of the present invention is to overcome the problems associated with prior methods and develop a method to determine the accuracy of liquid dispensing devices, particularly for very small volumes. Our solution was to develop a simple method where the dye can be generated *in situ* by adding a metal salt solution to a diluent containing an excess of ligands. When complexed to the metal, the initially colorless ligand becomes highly colored. Importantly, the complexation between the ligand and the metal must takes place rapidly and quantitatively. Hence, as long as a slight excess of ligand is present, one need not know the concentration of the dye with any degree of accuracy. By pipetting the highly water soluble salt solution rather than the dye, problems with the dye sticking to the pipette surface are eliminated. Furthermore, metal salt solutions have virtually identical viscosities to that of pure water.

Claims 48 and 49 recite the essential elements in the preceding paragraph. The advantages of generating the dye *in situ* is a significant advance that overcomes all methodology described in the prior art. Moreover, as pointed out clearly in the Hälg Declaration, the references taken alone or in combination do not teach or suggest the present invention. The Office Action relies on Lung as a primary reference. Lung does not contemplate generating chromophoric indicators

in situ. Furthermore, Lung does not teach or suggest a method for accurately determining the amount of a small volume dispensed by a pipette. The Office action alleges that "Lung et al discloses the basics of Applicants' claimed method steps, including the steps of introducing a known volume of colorimetric reagent." However, as already pointed out, claims 48 and 49 do not involve introducing colorimetric reagents but rather introduce metal ions to a diluent to form a colorimetric reagent.

The Examiner is respectfully directed to the case law, namely, that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further, as stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification." For the §103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988).

The office action contends that Bauer can be combined with Lung to render the present invention obvious. The Examiner relies on Bauer for allegedly teaching the chromophoric indicators utilized in the present invention. However, the mere fact that Bauer points out the existence of such chromophoric indicators is not relevant to the present invention. There is no motivation in Bauer or Lung for using the polydentate chromophoric ligands in making volumetric determinations. The Office Action points out that Bauer teaches that these chromophoric ligands are advantageous in that they are not affected by the outside environment. However, this point bears no relevance to the pending claims. The advantage, as taught in the present application, is that polydentate chromophoric ligands can be used for the *in situ* generation of dyes, thus allowing the accurate measurement of extremely small volumes. Neither Bauer nor Lung taken alone in combination teaches the in situ generation of chromophoric indicators to make small volume determinations. Moreover, there is no motivation for combining the two references to make volumetric determinations.

Independent claims 50 and 51 are directed to another embodiment of the invention. Here, the dye is chromophoric indicator is generated prior to being added to the diluent. The essential

feature of these claims involves the use of polydentate chromophoric ligands with a three-dimensional coordination geometry to generate the chromophoric indicator. The particular three-dimensional coordination geometry according to the present invention is preferred, because it greatly hinders adsorption of this type of molecule on apolar surfaces. Again, the fact that such indicators were known at the time of the present invention (e.g. Bauer) does not motivate one of ordinary skill in the art to u se these indicators in making volumetric determinations, such as those described in Lung. Lung relates to colorimetric reagents traditionally used in making volumetric determinations, such as cobalt sulfate. Lung does not provide any motivation for replacing these traditional chromophoric indicators with the polydentate chromophoric ligands with a three-dimensional coordination geometry used in the present invention. Lung does not point out any disadvantages of using these traditional chromophoric indicators that would motivate one skilled in the art to look elsewhere for better indicators. One can only determine the advantageous of using the polydentate chromogenic ligands applied in the present invention with hindsight. Applicants remind the Examiner that it is impermissible to engage in a hindsight reconstruction of the claimed invention, using the Applicant's structure as a template, and selecting elements from references to fill in the gaps. *Interconnect Planning*, 744 F.2d 1132, 1143 (Fed. Cir. 1985).

Even if a person of ordinary skill in the art would consult Bauer, there is no motivation for choosing the polydentate chromogenic ligands with the three-dimensional coordination geometry as presently claimed. As pointed out in the Hälg Declaration, there are literally thousands of possible polyvalent ion/ligand combinations mentioned in Bauer. Bauer does not show any advantage of using a chromogenic ligand with a three-dimensional coordination geometry. In actuality, the expressly pointed out examples for indicator molecules are all planar complexes with metal ions. Unlike the indicators used in the present invention, these have much lower extinction coefficients and tend to stick to the walls of a pipetter, which results in erroneous volume determinations. Thus, it is not proper to rely on Bauer in rejecting claims 50 or 51.

Consequently, reconsideration and withdrawal of the Section 103 rejections are earnestly requested.

REQUEST FOR AN INTERVIEW

If any issue remains as an impediment to allowance, a further interview with the Examiner and SPE are respectfully requested and the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In view of the remarks, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution.

Respectfully submitted,
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